REMARKS

Reexamination and reconsideration of the above-identified application are requested in view of the following amendments and remarks.

1. Claims

Claims 113, 114, 116-125 and 145-156 are pending. New claims 155 and 156 are supported in the specification as filed, e.g., at col. 2, paragraph 0011).

Applicants regret the inadvertent error in status identifier for Claim 116 in the amendment filed on 23 May 2006; as Claim 116 is further amended herein, the status identifier is shown above as "Currently Amended".

2. Claim rejections – 35 USC § 102(b)

Claims 113, 114, 116, 118, 119, 121, 145-148 and 150 stand rejected as anticipated by Cheever (US Patent No. 5,869,445). Applicants respectfully traverse this rejection.

The Office Action states that Cheever now reads on the present claims and dependent claims. The Office action states that claim 116 is drawn to a method for eliciting or enhancing an immune response by administering a composition comprising a protein comprising amino acid SEQ ID NO:7. Claim 113 is drawn to a similar method using a protein comprising SEQ ID NO:6.

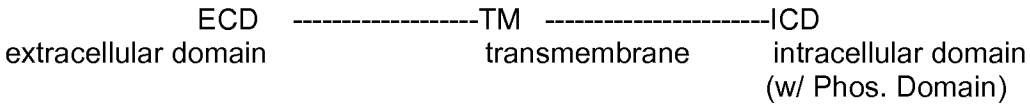
The Office Actions cites Cheever as disclosing methods for eliciting or enhancing an immune response using an isolated protein "comprising SEQ ID NO:6 or 7 (trx-human HER-2/neu polypeptide; Example 1); polypeptides using variants of the polypeptide of SEQ ID NO:2 from amino acid 676 through amino acid 1255…"

Applicants first respectfully dispute that Cheever teaches the use of a protein comprising the contiguous series of amino acids provided in SEQ ID NO:6 or 7, or that the trx-human HER-2/neu polypeptide used in Cheever's experiment 1 comprises the contiguous series of amino acids as provided in SEQ ID NO:6 or 7.

The present SEQ ID NO:6 is a polypeptide of 919 amino acids, made up of the 653 amino acid Extracellular Domain (ECD) joined directly to the 266 amino acid Phosphorylation Domain (PD) of human HER-2/neu. The amino acids present *between* the

ECD and PD in the intact HER-2/neu protein are omitted from SEQ ID NO:6. See the specification, e.g., at paragraphs 0090-0091.

As stated in the specification at paragraphs 008 and 009, the protein product of the human Her-2/neu gene is a transmembrane protein ("p185") that includes an extracellular domain (ECD), a transmembrane domain, and a carboxy terminal intracellular domain (ICD). The transmembrane domain is located between the ECD and ICD. The ICD includes a phosphorylation domain (PD).



The full length 1255 amino acid sequence of the human HER-2/neu protein is shown in Figure 7 (SEQ ID NO: 1). Figure 9 shows the amino acid sequence of the extracellular domain (ECD) of human HER-2/neu (SEQ ID NO: 3); the ECD is amino acids 1-653 of the full length protein. Figure 10 shows the amino acid sequence of the phosphorylation domain (PD) of the human HER-2/neu protein (SEQ ID NO:4); the PD is amino acids 990 -1255 of the full-length sequence. Figure 12 shows the amino acid sequence of SEQ ID NO:6 -- a protein comprising the human ECD joined to the human PD. The transmembrane domain that is located between the ECD and PD in the full-length human Her-2/neu protein is excluded from SEQ ID NO:6.

Figure 13 shows the amino acid sequence of a fusion protein comprising the human ECD and a truncated portion of the human phosphorylation domain (deltaPD) (SEQ ID NO: 7); the transmembrane domain and a portion of the naturally occurring PD are excluded from SEQ ID NO:7. Thus the present SEQ ID NO:7 is a polypeptide of 712 amino acids, made up of the Extracellular Domain (653 amino acids) joined directly to a 59 amino acid fragment of the Phosphorylation Domain (deltaPD). See the specification , e.g., at paragraphs 0096-0097.

Both SEQ ID NO:6 and 7 are "ECD-PD" fusion proteins. As stated in the specification, HER-2/neu ECD-PD fusion proteins comprise the extracellular domain and phosphorylation domain (or fragments thereof, e.g., deltaPD) of the HER-2/neu protein. Further "(t)he ECD-PD and ECD-deltaPD fusion proteins do not include a substantial portion

of the HER-2/neu transmembrane domain, and preferably do not include any of the HER-2/neu transmembrane domain" (final sentence of paragraph 0042, underlining added). Neither SEQ ID NO:6 or 7 include the transmembrane domain of HER-2/neu.

Cheever discloses the complete HER-2/neu protein sequence (SEQ ID NO:2, 1255 amino acids in length), and a preferred polypeptide (his "HER-2/neu polypeptide") having the amino acid sequence starting at HER-2/neu amino acid 676 (lysine) through the final amino acid (valine) at position 1255. See Cheever, e.g. at col. 2, lines 52-55; column 4 at lines 20-25. Neither the complete HER-2/Neu sequence (Cheever's SEQ ID NO:2) nor his preferred "HER-2/neu polypeptide" comprises a contiguous series of amino acids having the present SEQ ID NO:6 or 7.

At col. 4, lines 20-25, Cheever states that "HER-2/neu polypeptide as used herein, refers to a portion of the HER-2/neu protein (the protein also known as p185 or c-erbB2) having the amino acid sequence of SEQ ID NO:2 from lysine, amino acid 676, through valine, amino acid 1255" (col. 4, lines 20-25, underlining added).

The present SEQ ID NO:6 consists of amino acids 1-653 directly linked to amino acids 990- 1255 of human HER-2/Neu. Thus the present SEQ ID NO:6 does not include amino acids 676 – 989 of the complete HER-2/Neu protein, which Cheever requires by definition as part of his 'HER-2/neu polypeptide'. Thus the Cheever polypeptide, by definition, cannot comprise the contiguous amino acids of SEQ ID NO:6.

The present SEQ ID NO:7 includes amino acids 1-653 linked directly to amino acids 990-1048. Thus the present SEQ ID NO:7 does not include amino acids 676-989 or 1049-1255 of the complete HER-2/Neu protein, which Cheever requires by definition as part of his HER-2/neu polypeptide. Thus the Cheever polypeptide, by definition, cannot comprise the contiguous amino acids of SEQ ID NO:7.

Independent claims 113 and 116 have been amended for clarity to recite that the claimed protein comprises a contiguous amino acid sequence having SEQ ID NO:6 (or SEQ ID NO:7). The cited Cheever reference does not teach a protein consisting of, or comprising, a contiguous series of amino acids having SEQ ID NO:6 (or SEQ ID NO:7).

The Office Action further cites Cheever's trx-human HER-2/neu polypeptide (fusion protein of thioredoxin reductase plus "HER-2/Neu polypeptide") as described in Cheever's Example 1 as an example of an isolated protein "comprising SEQ ID NO:6 or 7". For the

same reasons as discussed above, Applicants respectfully dispute that this described protein consists of or comprises a contiguous series of amino acids having the present SEQ ID NO:6 or 7.

Withdrawal of the present rejection is respectfully requested.

3. Claims 113 and 117 – rejection under 35 USC s. 103: Cheever & Forsgren

The present Office Action maintains the rejection of Claims 113 and 117 as obvious over Cheever (US Patent 5,869,445) in view of Forsgren (WO91/18926). The previous Office Action cites Forsgren as teaching that lipidation ensures optimal presentation of an antigen, and concludes that it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to lipidate a protein to stimulate immune response with a reasonable expectation of success. Applicants respectfully traverse this rejection.

Applicants refer to the discussion above regarding why Cheever does not anticipate the present claims, and further submit that neither Cheever alone, nor the combination of Cheever and Forsgren, renders the present claims obvious.

Nothing in Cheever teaches or suggests to one of ordinary skill in the art that a peptide having a contiguous sequence of amino acids of SEQ ID NO:6 (or 7) would be useful in the present methods. The preferred HER-2/Neu polypeptide taught by Cheever (aa 676-1255) includes a segment of the HER-2/Neu sequence that is omitted from the current SEQ ID NO:6 or 7. Cheever teaches a polypeptide having amino acids 676-1255 of HER-2/neu; nothing in Cheever teaches or suggests omitting amino acids 676-989 (more than half of Cheever's "preferred polypeptide") to obtain a polypeptide with immune enhancing properties.

Forsgren does not teach HER-2/neu polypeptides.

Applicants respectfully submit that the combination of Cheever and Forsgren does not render the present claims obvious, and request withdrawal of the present rejection.

4. Rejection under 35 USC s. 103: Cheever & Garcon

The present Office Action maintains the rejection of Claims 113, 116, 119, 120, 122-124, 149, and 151-153 as obvious over Cheever (US Patent 5,869,445) in view of Garcon

(WO95/17210). The previous Office Action cites Garcon as teaching the use of adjuvants with vaccines based on recombinant proteins, and concludes that it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to produce a composition comprising the claimed elements. Applicants respectfully traverse this rejection.

Applicants refer to the discussions above regarding why Cheever does not anticipate or render obvious the present claims, and further submit that the teachings of Garcon do not remedy the deficiencies of the Cheever reference. Garcon does not teach the use of HER-2/neu polypeptides.

Applicants respectfully submit that the combination of Cheever and Garcon does not render the present claims obvious, and request withdrawal of the present rejection.

5. Rejection under 35 USC s. 103: Cheever and Krieg

The present Office Action maintains the rejection of Claims 113, 116, 125, and 154 as obvious over Cheever (US Patent 5,869,445) in view of Krieg (WO96/02555). The previous Office Action cites Krieg as teaching the use of CpG-containing nucleotides, and concludes that it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use a known immune stimulatory molecule to stimulate immune response. Applicants respectfully traverse this rejection.

Applicants refer to the discussions above regarding why Cheever does not anticipate or render obvious the present claims, and further submit that the teachings of Krieg do not remedy the deficiencies of the Cheever reference. Krieg does not teach the use of HER-2/neu polypeptides.

Applicants respectfully submit that the combination of Cheever and Krieg does not render the present claims obvious, and request withdrawal of the present rejection.

6. Rejection under 35 USC s. 112 - Indefinite

Claims 113 and 116 stand rejected as indefinite for the recitation of "capable of producing an immune response". The Office Action states that "capable" is not a positive limitation for the molecule actually possessing the claimed property of producing an immune response.

The Examiner states that "Applicant's amendments to the claims have necessitated" this new ground for rejection. Applicants respectfully note, however, the phrase "capable of producing an immune response" was present in Claim 113 as previously filed, and submit that Applicant's amendments did not necessitate the present new rejection.

The claims have presently been amended, above, and Applicants submit that the present amendment obviates the indefiniteness rejection.

7. 35 USC 112, first paragraph: Enablement

Claims 113-125 and 145-154 stand rejected as non-enabled. Applicants respectfully traverse this rejection.

The Office Action states that the specification is enabling "for methods of eliciting an immune response using a Her-2/neu fusion protein comprising SEQ ID NOS:6 or 7 to stimulate T-cell proliferation and cytotoxicity and to induce B cells to produce an antibody, for use in treating malignancies such as breast, ovarian, colon, lung and prostate cancers", but further states that the specification does not enable "using the method to elicit a specific immune response against just any disorder much less just any cancer."

However, the present claims do not recite treatment of a particular disorder or cancer. The claims do not recite eliciting an immune response "against just any disorder". The present claims recite a method for "eliciting or enhancing an immune response to HER-2/neu protein" using a recited construct. The Examiner has not questioned whether it would require undue experimentation by one skilled in the art to make the present constructs, and states that the use of the claimed methods is enabled to elicit an immune response to HER-2/neu protein, but concludes that this enablement is somehow limited to certain uses (uses that are not recited in the claims).

As stated in MPEP the enablement requirement requires that "the specification describe how to make and how to use the invention. The invention … is that defined by the claim(s) of the particular application or patent." Further, "(t)he information contained in the disclosure must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention." (MPEP s.2164, underlining added). The MPEP cautions that "(o)ffice personnel should also be especially careful not to read into a claim unclaimed results, limitations or embodiments of an invention." See MPEP s.2107.02 *citing Carl Zeiss*

Stiftung v. Renishaw PLC, 20 USPQ2d 1094 (Fed. Cir. 1991); *In re Krimmel,* 130 USPQ 215 (CCPA 1961).

The Office Action first states that the claims "are drawn to a general method for eliciting or enhancing an immune response in warm-blooded animals" but then states that the claims "encompass" using the immune response to treat any kind of disorder. Applicants respectfully question whether the present rejection improperly combines elements of both the enablement and utility requirements. The Office Action concludes that the specification "does not enable or support using the method or enhancing or eliciting the immune response for anything but treating breast, ovarian, colon, lung and prostate cancers" and that "absent … evidence that the claimed methods are effective for eliciting or enhancing a specific immune response in a subject where there is a practical endpoint for other than affecting breast, ovarian, colon, lung and prostate cancer, the enablement provided by the specification is not commensurate in scope with the claimed invention." (underlining added).

Enablement does not require that the specification enable every "practical endpoint" for the claimed invention. What must be enabled is the claimed invention. The present claims recite a method of eliciting an immune response using a particular HER-2/neu construct. Applicants realize that the specification must enable both "making" and "using" the claimed invention. However, the Examiner has not questioned the ability of one skilled in the art to make the current constructs, or to use the current constructs to enhance or elicit an immune response to HER-2/neu (other than questioning the route of administration, which is addressed below). The specification describes methods of detecting an immune response to HER-2/neu (see e.g., paragraph 0224). The enablement inquiry must focus on the claimed subject matter, not the *potential outcome* of using the claimed method in various settings.

Route of administration: The claims recite administration of a HER-2/neu construct to a warm-blooded animal. On page 12, the Office Action states that (i) it would take undue experimentation to determine what route of administration would result in an immune response using the claimed polypeptide, (ii) that there are multiple routes of administration known in the art (e.g., intravenous, dermal, etc), and (iii) that "the amount of direction or guidance presented in the specification is limited."

The MPEP at s.2164.04 states that the Examiner has the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention, and must explain why the truth or accuracy of any statement is doubted and provide evidence in support of the non-enablement rejection. It is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright,* 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Applicants submit that the PTO has not met the initial burden of setting forth a reasonable explanation of lack of enablement regarding a route of administration.

The rejection regarding 'route of administration' appears to be based on a perceived lack of guidance in the specification. However, the specification addresses routes of administration, e.g., at paragraph 0206, 0213, 0238, and 0243. At paragraph 0243 it is noted that routes of administration will vary depending on the individual being treated, but may be established using standard techniques. The Office Action does not provide any evidence to suggest that it would require *undue experimentation* to determine a successful route of administration (particularly in view of the specification's discussion regarding detection of immune response to the administered HER-2/neu construct, see e.g., paragraph 0224).

It is well established that a claimed invention may be enabled even though some experimentation is required, "the issue is whether the amount of experimentation is 'undue'". *In re Vaeck,* 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Whether it would be time-consuming for one skilled in the art to test and refine various routes of administration is not the issue; the issue is whether one skilled in the art could follow the teachings of the specification and the art to do so. As noted by the Patent and Trademark Appeals Board:

> The test is not merely quantitative, **since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed** to enable the determination of how to practice a desired embodiment **of the invention claimed**.

Ex Parte Jackson, 217 USPQ 804, 807 (1982) (emphasis added).

Applicants submit that the Examiner has not adequately explained why one skilled in the art would have undue difficulty in identifying routes of administration.

In view of the above, withdrawal of the current rejection is requested.

8. 35 USC 102: Laus

Claims 113, 114, 116, 118, 145, and 147 stand rejected as anticipated by Laus et al (US 5,976,546). This rejection is respectfully traversed.

The Office Action cites Laus as disclosing a GM-CSF-HER2 fusion protein using the extracellular domain (amino acids 1-652) of HER-2, and the Office Action refers to a copy of a sequence alignment for claimed SEQ ID Nos:6 and 7 with the sequence of Laus.

Laus et al. describe a fusion protein incorporating the Extracellular Domain (ECD) of HER-2/neu (stated to be amino acids 1-652 at col. 8, line 59 of the '546 patent, but shown as amino acids 1-653 in SEQ ID NO:4 of Laus).

As discussed above, the present SEQ ID NO:6 is a polypeptide of 919 amino acids, made up of the Extracellular Domain joined directly to the Phosphorylation Domain of human HER-2/neu. See the specification, e.g., at paragraphs 0090-0091. The present SEQ ID NO:7 is a polypeptide of 712 amino acids, made up of the Extracellular Domain (653 amino acids) joined directly to a 59 amino acid fragment of the Phosphorylation Domain (the deltaPD). See the specification, e.g., at paragraphs 0096-0097.

Applicants note that the sequence alignment provided includes only a portion of the present SEQ ID NO:6 and 7 (only the first 667 amino acids of the 919 or 712 amino acid sequence, respectively), and only a portion of SEQ ID NO:4 of Laus (the first 665 amino acids of 782). Comparing the full SEQ ID NO:4 of Laus to the present SEQ ID NO:6 (or 7) shows that while each sequence includes the extracellular domain of HER-2/neu, the polypeptides do not have the same contiguous amino acid sequence. Further, Applicants submit that nothing in Laus teaches or suggests a HER-2/neu construct comprising the Extracellular Domain joined directly to the Phosphorylation Domain (or any fragment of the Phosphorylation Domain).

Inasmuch as the present claims recite use of a polypeptide comprising a contiguous sequence of amino acids having SEQ ID NO:6 (or 7), and Laus et al. do not disclose either of SEQ ID NO:6 or 7, Applicants request withdrawal of the present rejection.

Conclusion

Applicants respectfully submit that the present application is in condition for allowance. If the Examiner believes a telephone conference would expedite prosecution of the application, please do not hesitate to call the undersigned at 919-483-1012.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

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